PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Davies Collison Cave
Level 15
1 Nicholson Street
MELBOURNE VIC 3000

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *day/month/year*	- 5 AUG 2004
Applicant's or agent's file reference 12185280/TDO/LM	**IMPORTANT NOTIFICATION**

International Application No.	International Filing Date	Priority Date
PCT/AU2003/000388	28 March 2003	28 March 2002

Applicant
MEDVET SCIENCE PTY.LTD. et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

Name and mailing address of the IPEA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	M. Ong Telephone No. (02) 6283 2491

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 12185280/TDO/LM	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU2003/000388**	International Filing Date *(day/month/year)* 28 March 2003	Priority Date *(day/month/year)* 28 March 2002
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] A61K 38/43, A61K 38/18, A61K 38/19, A61K 38/00, A61P 29/00, A61P 35/00, A61 37/00		
Applicant MEDVET SCIENCE PTY.LTD. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of **6** sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of **2** sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [X] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand 17 October 2003	Date of completion of the report 9 July 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **M. Ong** Telephone No. (02) 6283 2491

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/000388

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-58,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☒ the claims, pages **59-64** , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

☒ the drawings, pages **1/21-19/21,** as originally filed,
pages , filed with the demand;
pages **20/21, 21/21,** received on **7 July 2003** with the letter of **7 July 2003**

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims **4, 5, 9, 10,11, 15, 16, 19, 26, 27, 31, 32, 35, 42, 43, 48, 49**	**YES**
	Claims **1-3, 6-8, 12-14, 17, 18, 20-25, 28-30, 33, 34, 36-41, 44, 45-47**	**NO**
Inventive step (IS)	Claims **48, 49**	**YES**
	Claims **1-47**	**NO**
Industrial applicability (IA)	Claims **1-49**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1: WO 1999/12533 A
D2: WO 2001/85953 A
D3: Blaukat, A et al.
D4: Machwate, M et al.
D5: Cuvillier, O et al.
D6: Johnson, KR et al.
D7: Maceyka, M et al.

New Citation
D8: Xia, P et al. Sphingosine kinase interacts with TRAF2 and dissects tumour necrosis factor-α signalling. Journal of Biological Chemistry, 8 March 2002, vol. 277(10), pages 7996-8003

Novelty (N): Claims 1-47

D1 discloses a method and agents for modulating cellular activity. Methods of treatment or prophylaxis of a disease condition involving inflammatory mechanisms using an agent capable of modulating one or more components of a sphingosine kinase signalling pathway wherein the modulation results in modulation of adhesion molecule expression, is taught. In particular, HDL treatment of endothelial cells is disclosed to substantially blunt the amplitude and duration of Sph-1-P formation by inhibiting sphingosine kinase activity. This results in the blunting of MEK/ERK activation and NF-κB nuclear translocation thereby reducing adhesion protein expression. N,N-dimethyl sphingosine decreases TNF-α induced adhesion protein expression and mRNA levels by competitively inhibiting sphingosine kinase activity. This is relevant to claims 1-3, 6, 7, 9, 12-14, 17, 18, 20, 21-25, 28-30, 33, 34, 36-41, 44 and 45.

D2 teaches a method of modulating the growth of a cell by contacting the cell with an effective amount of an agent under conditions to modulate the functional activity of sphingosine kinase (SPK). A method of down-regulation of cell proliferation wherein the cell is a neoplastic cell, is disclosed. Antagonists of sphingosine kinase include N,N-dimethyl sphingosine and DL-threo-dihydrosphingosine. Chemical agonists include chemical and functional equivalents of sphingokinase nucleic acid or protein molecules or derivatives produced by common molecular techniques. This is relevant to claims 1-3, 9, 12-14, 20-24, 28-30, 36-38, 44 and 45.

D3 discloses the activation of sphingosine kinase by bradykinin B_2 receptor via activation of ERK/MAP kinase. DL-threo-dihydrosphingosine, a known sphingosine kinase inhibitor was taught to block S1P generation and reduced the B_2 receptor induced ERK and ERK/MAP kinase activation in a dose dependent manner. This is relevant to claims 1-3, 6-9, 12-14, 17-20, 28-30, 33-36, 44 and 45.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

D4 teaches the stimulation of cytosolic sphingosine kinase activity by forskolin whilst PD98059, a selective inhibitor stimulates apoptosis in two osteoblastic cell lines. N,N-dimethyl sphingosine, another inhibitor of SPK was shown to completely reverse the antiapoptotic effect of forskolin. Other activators of SPK taught include PDGF, serum and 12-O-tetradecanoylphorbol-13-acetate (TPA) and cAMP. This is relevant to claims 1-3, 6-9, 11-14, 17-22 and 27.

D5 discloses the positive regulation of SPK by 12-O-tetradecanoylphorbol-13-acetate, and is negatively regulated by dimethyl sphingosine. It is further taught that S-1P generated through a protein kinase C mediated activation of SPK, can inhibit apoptosis. This relevant to claims 1-3 and 12-14.

D8 teaches TNF or overexpression of TRAF2 was capable of activating SPK and that TNF-induced SPK activation was blocked by the dominant-negative TRAF2. SPK mutants lacking either the TRAF2-binding motif or enzyme catalytic activity abrogated the effect of TRAF2. This is relevant to claims 1-3, 46 and 47.

Therefore it is considered that claims 1-3, 6-8, 12-14, 17, 18, 20-25, 28-30, 33, 34, 36-41, 44 and 45-47 do not meet the requirements of Article 33(2) PCT with regard to the requirement for novelty in view of the disclosures of D1-D5 and D8.

Claims 4, 5, 9-11, 15, 16, 19, 26, 27, 31, 32, 35 42, 43, 48 and 49 meet the criteria set forth in PCT Article 33(2) for novelty. The prior art published before the priority date does not disclose the modulation of sphingosine kinase functional activity where the modulation of phosphorylation of the sphingosine kinase activity occurs at S^{225}. The prior art, further do not disclose the modulation of said phosphorylation as modulation of proline-directed protein kinase catalysed phosphorylation ie. ERK2. Further, use of U0126 and PD98059 for the treatment and/or prophylaxis of a condition characterised by aberrant , unwanted or otherwise inappropriate sphingosine kinase functional activity where modulation of phosphorylation of sphingosine kinase is warranted were not disclosed.

Inventive Step (IS): Claims 1-47
As above.

Industrial Applicability: Claims 1-47
Claims 1-47 have industrial applicability

Please see indication contained in Box VI, "Certain documents cited" with regard to D6 and D7.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 2002/098458	12 December 2002	3 June 2002	7 June 2001

WO 2002/098458 discloses a method of modulating cytokine-induced cellular activity to modulate interaction of SPK with a TRAF whereby inducing SPK and TRAF association with an agent that binds, links or otherwise associates with the C-terminal region of sphingosine kinase, up-regulates cellular activity and, antagonising said association down-regulates cellular activity. Treatment and/or prophylaxis of conditions characterised by aberrant, unwanted or otherwise inappropriate cytokine-mediated cellular activity with said agent is further taught.

Please refer to the supplemental Box for further comments on D6 and D7.

With regard to the document listed in Box VI, this document was published after the priority date of the present application but would otherwise be considered of particular relevance.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

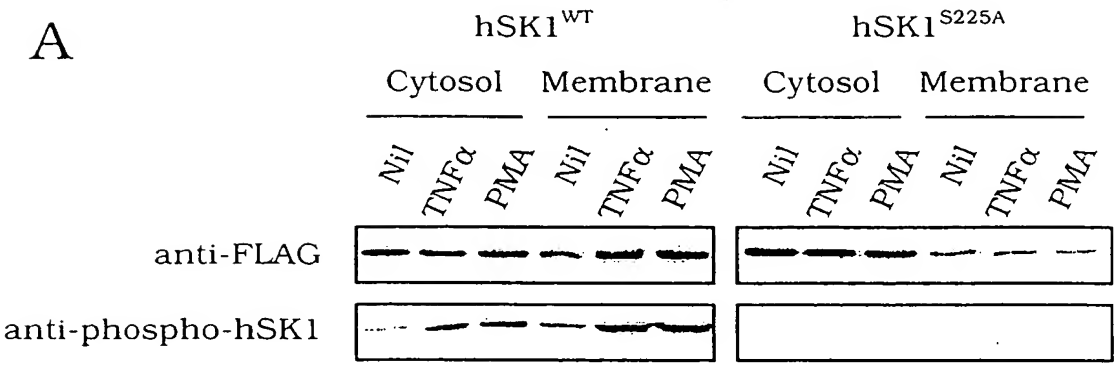
Continuation of VI

D6 teaches the regulation of SPK with the protein kinase C (PKC) activator, phorbol 12-myristate 13-acetate (PMA) through the phosphorylation of SPK.

D7 discloses the known SPK inhibitors threo-dihydrosphingosine (DHS) and NN-dimethylsphingosine (DMS) as well as a list of agonist, amongst others, G-protein coupled receptors (GPCR), including acetylcholine, prosaposin and others. Agonists of growth factor receptor tyrosine kinase are also taught to activate SPK. It is further disclosed that S1P activates ERK in Swiss 3T3 fibroblasts and TNF-α activates ERK in a SPK -dependent manner in U937 leukemia cells. Inhibition of ERK activity by PD98059 is disclosed.

Please note that this opinion has been based on the assumption that the claimed subject matter of the present application validly derives its priority claim. However, D6 and D7 would be relevant to claims 1-3, 6-14, 17-25, 27-30, 33, 41 and 43-45 if the present application is found to not validly claim its priority.

Under the PCT, novelty is considered only in respect of documents published before the priority date. The relevance of a document published after the priority date is dependent upon national law. Such documents are excluded from consideration in preliminary examination, under the PCT Guidelines but have been included here for information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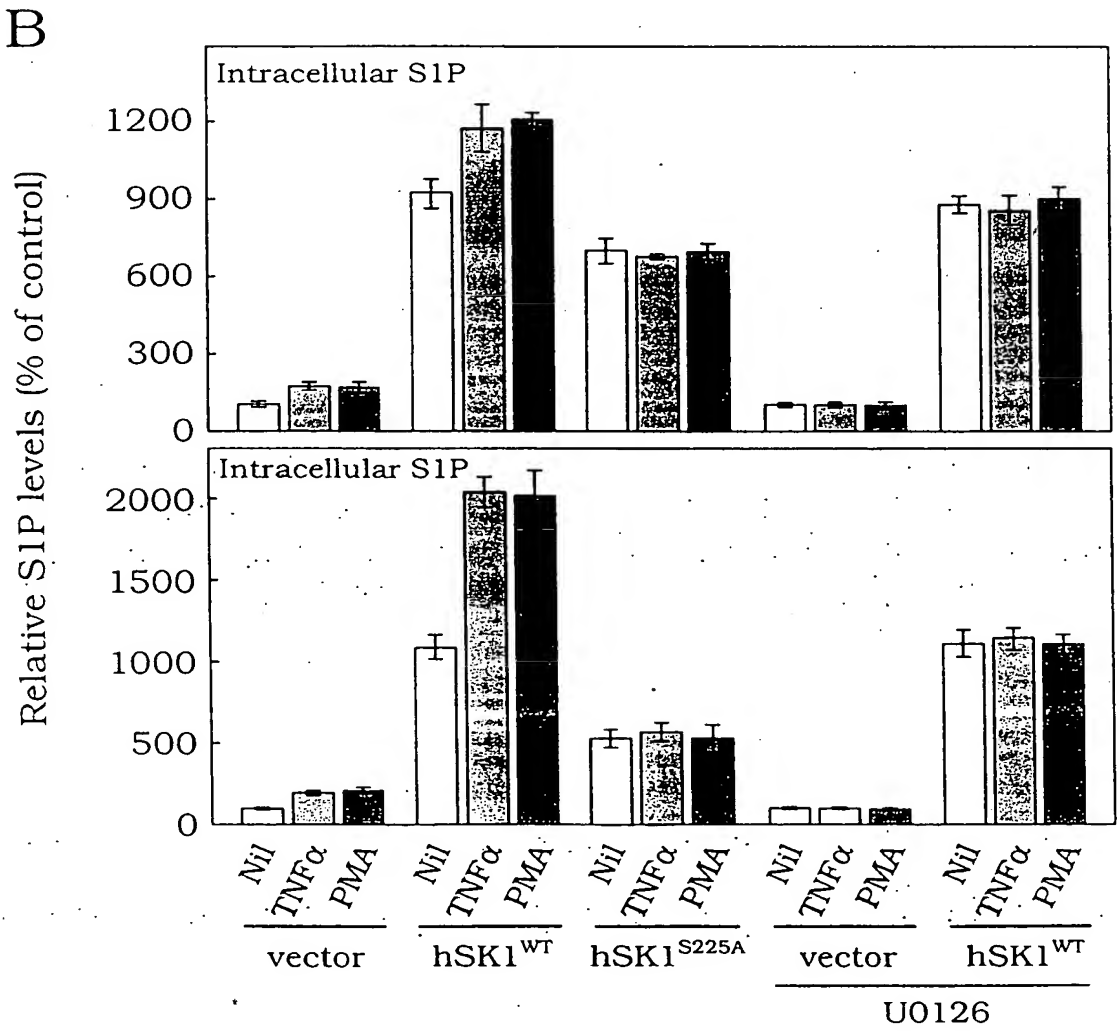
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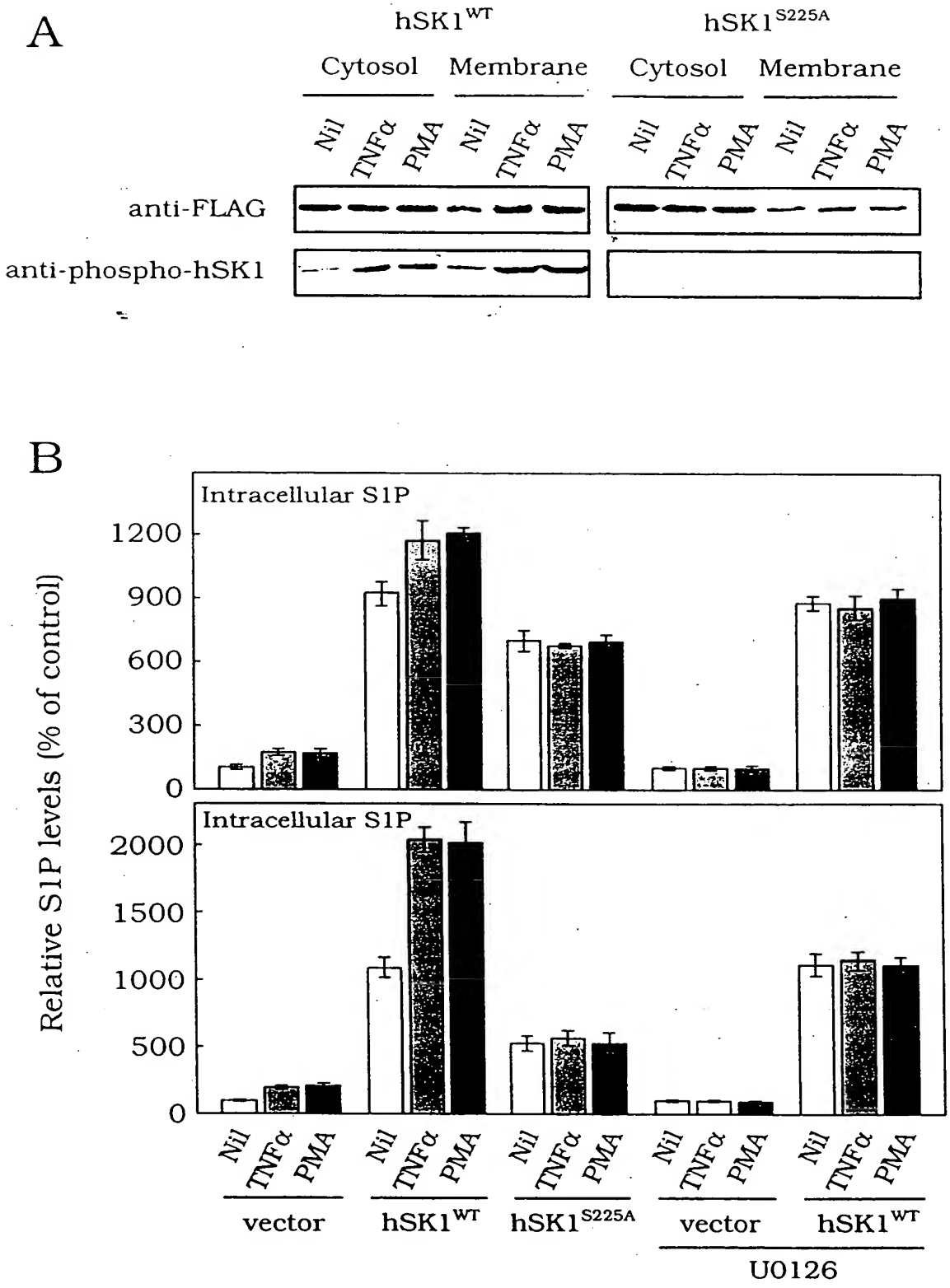
U0126

Figure 18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U0126

Figure 18